1 410 275

PATENT SPECIFICATION

(11) 1 410 275

(21) Application No. 34300/73 (22) Filed 18 July 1973
(61) Patent of Addition to No. 1 397 697 dated 31 May 1973
(31) Convention Application No. 73249/72 (32) Filed 20 July 1972 in
(33) Japan (JA)
(44) Complete Specification published 15 Oct. 1975
(51) INT CL² C07C 59/26; A61K 31/19, 31/22; C07C 79/35
(52) Index at acceptance
C2C 1175 220 221 225 226 227 22Y 231 237 239 240
261 292 29Y 30Y 313 31Y 332 338 351 355 35Y
364 366 367 368 36Y 389 38Y 490 491 496 499
500 50Y 621 624 625 628 634 655 658 65X 661
662 668 682 699 790 79Y BT MK UR

(19)

(54) PHENOXYCARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION, AND COMPOSITIONS CONTAINING THEM

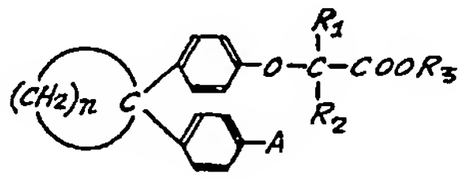
(71) We, SUMITOMO CHEMICAL COMPANY LIMITED, a corporation organised under the laws of Japan of 15 Kitahama-5-chome, Higashi-ki, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel anti-atherosclerosis agents. More particularly, the invention pertains to novel substituted phenoxycarboxylic acid derivatives which are found to be useful for lowering elevated levels of cholesterol or lipids in the blood.

Atherosclerosis is an adult disease for which there is no known satisfactory cure. Although the cause of atherosclerosis is not yet known in spite of academic discussions, it has broadly been recognized that one of the most significant histo-pathological manifestations of atherosclerosis is the deposition of cholesterol or lipids in the blood.

A number of experimental and clinical facts have been reported, which indicate that the reduction of elevated blood cholesterol or lipid level is considered extremely important for the prevention of atherosclerosis.

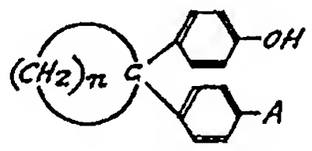
The present invention provides a substituted phenoxycarboxylic acid derivative of the formula,



(I)

wherein R_1, R_2 and R_3 are each independently a hydrogen atom or a C_1—C_4 alkyl group; n is 4, 5 or 6; and A is a hydrogen atom, a halogen atom, a C_1—C_4 alkyl group, a C_1—C_4 alkoxy group, an optionally substituted aryloxy group, an aralkoxy group or a C_2—C_5 alkanoyloxy group, or a pharmaceutically acceptable salt thereof.

The present invention further provides a process for producing a substituted phenoxycarboxylic acid derivative within the formula (I), which includes reacting a phenol derivative of the formula,



(II)

wherein A and n are as defined above, with chloroform and a carbonyl compound of the formula,

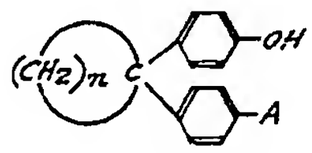
(III)

$$R_1—CO—R_2$$

wherein R_1 and R_2 are as defined above, in the presence of an alkali to yield a substituted phenoxycarboxylic acid derivative of the formula (I) in which R_3 is specifically a hydrogen atom.

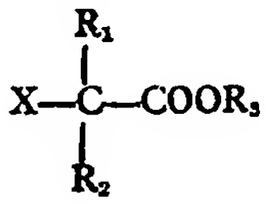
[*Price 33p*]

A phenoxycarboxylic acid derivative of the formula (I) can also be prepared by a process within the present invention which includes reacting a phenol derivative of the formula,



(II)

wherein A and n are as defined above, with a carboxylic acid derivative of the formula,



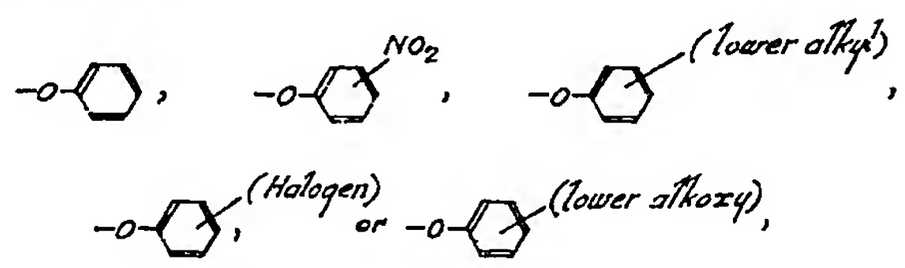
(IV)

wherein R_1, R_2 and R_3 are as defined above; and X is a halogen atom or a hydroxyl group, to yield the substituted phenoxycarboxylic acid derivative of the formula (I), and then, optionally esterifying or hydrolyzing the resultant substituted phenoxycarboxylic acid derivative to a yield a corresponding ester or free acid respectively.

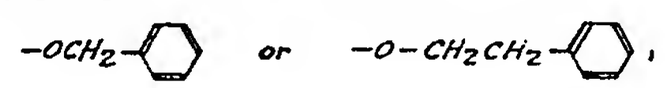
The present invention furthermore provides a cholesterol lowering composition containing, as an active ingredient, a substituted phenoxycarboxylic acid derivative of the formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, and a method of lowering an elevated cholesterol or lipid level in an animal which includes administering to the animal such a substituted phenoxycarboxylic acid derivative or pharmaceutically acceptable salt thereof. The term "animal" used herein excludes human beings.

It appears that there is no mention of compounds of the formula (I) in the literature.

In compounds of the present invention, the alkyl group within the definitions of R_1, R_2, R_3 and A may be methyl, ethyl, n- or iso-propyl or n-, iso- or t-butyl, the alkoxy group within the definition of A may be methoxy, ethoxy, n- or iso-propoxy or n-, iso- or t-butoxy, the halogen atom within the definition of A may be chlorine, bromine or iodine, examples of the optionally substituted aryloxy group within the definition of A are the following phenoxy groups



examples of the aralkoxy group within the definition of A are



and examples of the C_2—C_5 alkanoyloxy group within the definition of A are CH_3COCH_2O—, $CH_3COCH_2CH_2O$— or $CH_3CH_2COCH_2O$—. A substituted phenoxycarboxylic acid derivative of the formula (I) of the present invention can be produced by reacting a phenol derivative of the formula (II) with chloroform and a carbonyl compound of the formula (III) in the presence of an alkali, and then, optionally esterifying the resultant substituted phenoxycarboxylic acid. Usually, in order to carry out this reaction, at least 1 mole of chloroform is added dropwise to a mixture containing 1 mole of the phenol derivative of the formula (II) and at least 1 mole of the carbonyl compound of the formula (III) in the presence of at least 3 moles of the alkali. Examples of the alkali used are sodium hydroxide and potassium hydroxide. This reaction can be carried out at a temperature of 10°—150°C., usually at 15°—60°C. for a period of time of 0.5—40 hours. The reaction may be carried out optionally in the presence of an inert reaction medium or optionally in the presence of an excess of chloroform and/or the carbonyl compound of the formula (III). Examples of the inert reaction medium are dioxane, benzene, and toluene.

The substituted phenoxycarboxylic acid derivatives of the formula (I) can optionally be esterified by a conventional esterification method, for example, by reaction with

an alcohol, diazomethane, a dialkyl sulfate, an alkyl halide, or an alkyl halogenosulfite.

Alternatively, in a process within the present invention, the substituted phenoxycarboxylic acid derivative of the formula (I) can be prepared by reacting a phenol derivative of the formula (II) with a carboxylic acid derivative of the formula (IV).

Preferred methods of carrying out this process of the present invention are explained below in more detail.

When X in the formula (IV) represents a halogen atom such as chlorine, bromine or iodine, the following procedure is preferably adopted:

The phenol derivative of the formula (II) is suspended or dissolved in an inert solvent such as benzene, toluene, methanol, ethanol, ether, dioxane, dimethylsulfoxide, or N,N-dimethylformamide, and then treated with a suitable basic compound such as an alkali metal hydroxide, alkali metal alcoholate, metallic alkali metal, alkali metal hydride, organic tertiary amine such as pyridine, triethylmine, dimethylaniline, or diethylaniline, or an alkali metal carbonate. The carboxylic acid derivative of the formula (IV) is then added dropwise to the mixture. The reaction can be carried out at a temperature of 10°—150°C. for a period of time of 0.5—10 hours. Subsequently, the reaction product is subjected to the usual procedures for isolating a crude product, which is then purified.

When X in the formula (IV) represents a hydroxyl group, an acid catalyst such as sulfuric acid, or p-toluene-sulfonyl chloride can be used, whereby the desired acid or ester derivative can be obtained.

If the product obtained is an acid (i.e. R_3 in the formula (I) is a hydrogen atom), it may be converted into an ester of the formula (I) in which R_3 is a lower alkyl group as described above. Alternatively, if the product is an ester of the formula (I) in which R_3 is a lower alkyl group, the ester may further be hydrolyzed with an alkali or acid to obtain an acid of the formula (I) in which R_3 is a hydrogen atom, or a salt thereof.

In the present invention, the substituted phenoxycarboxylic acid derivative of the formula (I) in which R_3 is a hydrogen atom may be converted into a salt by treating it with an alkali. An alkali metal salt can be obtained by treating the substituted phenoxycarboxylic acid derivative of the formula (I) in which R_3 is a hydrogen atom with, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate or ammonia, or with an alcoholate of an alkali metal such as sodium methylate in an organic solvent, preferably in a lower alkanol such as methanol or ethanol, or with the hydroxide, carbonate or bicarbonate of an alkali metal in an organic solvent, preferably in acetone or methanol, optionally in the presence of a small amount of water. The alkali metal salt thus obtained can be converted into an alkaline earth metal salt by treating it with a salt of an alkaline earth metal such as calcium chloride.

In some cases, it is difficult to purify the substituted phenoxycarboxylic acid derivative of the formula (I) in which R_3 is a hydrogen atom by recrystallization. In these cases, the acid is purified after esterification by column chromatography, whereby the ester can easily be purified. The ester thus purified is then hydrolyzed to obtain the desired acid in high purity.

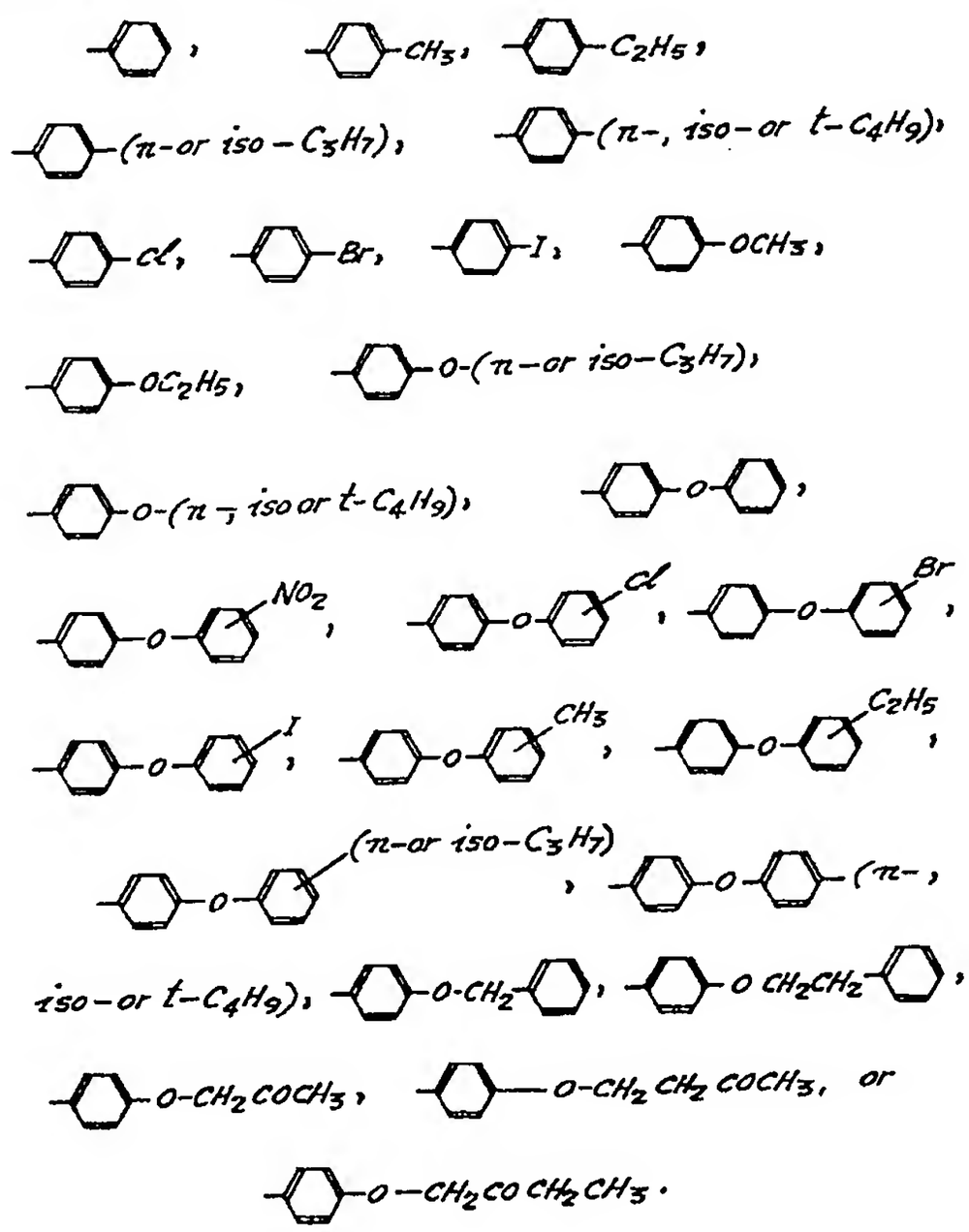
The phenol derivatives represented by the formula (II) which are used in a process within the present invention can easily be obtained by a known process disclosed in J.A.C.S. *60*, 59 (1938), in which a phenylcyclohexyl alcohol is condensed with phenol in the presence of an acid catalyst such as sulfuric or phosphoric acid.

Specific examples of the compounds within the scope of the present invention are as follows:

Cyclo C_5H_8—1,1—(B)—p—$C_6H_4OCH_2CO_2H$
Cyclo C_5H_8—1,1—(B)—p—$C_6H_4OCHCH_3CO_2H$
Cyclo C_5H_8—1,1—(B)—p—$C_6H_4OC(CH_3)_2CO_2H$
Cyclo C_5H_8—1,1—(B)—p—$C_6H_4OCHC_2H_5CO_2H$
Cyclo C_5H_8—1,1—(B)—p—$C_6H_4OC(CH_3)(C_2H_5)CO_2H$
Cyclo C_5H_8—1,1—(B)—p—$C_6H_4OCH(n—C_3H_7)CO_2H$
Cyclo C_5H_8—1,1—(B)—p—$C_6H_4OCH(iso—C_3H_7)CO_2H$
Cyclo C_5H_8—1,1—(B)—p—$C_6H_4OC(C_2H_5)_2CO_2H$
Cyclo C_5H_8—1,1—(B)—p—$C_6H_4OCH(n—C_4H_9)CO_2H$
Cyclo C_5H_8—1,1—(B)—p—$C_6H_4OCH(iso—C_4H_9)CO_2H$
Cyclo C_5H_8—1,1—(B)—p—$C_6H_4OCH(t—C_4H_9)CO_2H$
Cyclo C_6H_{10}—1,1—(B)—p—$C_6H_4OCH_2CO_2H$
Cyclo C_6H_{10}—1,1—(B)—p—$C_6H_4OCHCH_3CO_2H$
Cyclo C_6H_{10}—1,1—(B)—p—$C_6H_4C(CH_3)_2CO_2H$
Cyclo C_6H_{10}—1,1—(B)—p—$C_6H_4OCHC_2H_5CO_2H$
Cyclo C_6H_{10}—1,1—(B)—P—$C_6H_4O(CH_3)(C_2H_5)CO_2H$

Cyclo C_6H_{10}—1,1—(B)—p—$C_6H_4OCH(n—C_3H_7)CO_2H$
Cyclo C_6H_{10}—1,1—(B)—p—$C_6H_4OCH(iso—C_3H_7)CO_2H$
Cyclo C_6H_{10}—1,1—(B)—p—$C_6H_4OC(C_2H_5)_2CO_2H$
Cyclo C_6H_{10}—1,1—(B)—p—$C_6H_4OCH(n—C_4H_9)CO_2H$
Cyclo C_6H_{10}—1,1—(B)—p—$C_6H_4OCH(iso—C_4H_9)CO_2H$
Cyclo C_6H_{10}—1,1—(B)—p—$C_6H_4OCH(t—C_4H_9)CO_2H$
Cyclo C_7H_{12}—1,1—(B)—p—$C_6H_4OCH_2CO_2H$
Cyclo C_7H_{12}—1,1—(B)—p—$C_6H_4OCHCH_3CO_2H$
Cyclo C_7H_{12}—1,1—(B)—p—$C_6H_4OC(CH_3)_2CO_2H$
Cyclo C_7H_{12}—1,1—(B)—p—$C_6H_4OCHC_2H_5CO_2H$
Cyclo C_7H_{12}—1,1—(B)—p—$C_6H_4OC(CH_3)(C_2H_5)CO_2H$
Cyclo C_7H_{12}—1,1—(B)—p—$C_6H_4OCH(n—C_3H_7)CO_2H$
Cyclo C_7H_{12}—1,1—(B)—p—$C_6H_4OCH(iso—C_3H_7)CO_2H$
Cyclo C_7H_{12}—1,1—(B)—p—$C_6H_4OCH(C_2H_5)_2CO_2H$
Cyclo C_7H_{12}—1,1—(B)—p—$C_6H_4OCH(n—C_4H_9)CO_2H$
Cyclo C_7H_{12}—1,1—(B)—p—$C_6H_4OCH(iso—C_4H_9)CO_2H$
Cyclo C_7H_{12}—1,1—(B)—p—$C_6H_4OCH(t—C_4H_9)CO_2H$
Methyl esters of the above-mentioned acids
Ethyl esters of the above-mentioned acids
n-Propyl esters of the above-mentioned acids
iso-Propyl esters of the above-mentioned acids
n-Butyl esters of the above-mentioned acids
iso-Butyl esters of the above-mentioned acids
t-Butyl esters of the above-mentioned acids
Na salts of the above-mentioned acids
K salts of the above-mentioned acids
Ca salts of the above-mentioned acids
Mg salts of the above-mentioned acids
NH_4 salts of the above-mentioned acids
Al salts of the above-mentioned acids

In the above exemplified compounds, " B " means a group of the formula,



The cholesterol-lowering agents of the invention may, for example, be orally administered. Usually the amount orally administered is 0.01 g—10 g. per day/human adult, and preferably 0.05 g—3 g. per day/human adult. The cholesterol-lowering agents may be in any suitable conventional form for oral administration. Thus they may be encased in a capsule, or they may be in liquid form, tablet form, or in the form of a powder. In preparing the agents in these various forms, the active compound may be mixed with or impregnated in a pharmacentially acceptable carrier, for example, lactose, potato starch, corn starch, cellulose derivatives, gelatin, corn oil or cotton seed oil etc.

The cholesterol-lowering activity of the present compounds in mice was tested by injecting them intravenously with 500 mg/kg of Triton WR 1339 (Trademark for oxyethylated tert-octylphenol formaldehyde polymer manufactured by Rohm & Haas Co., U.S.A.).

The test compounds were orally administered in a dose of 12.5 mg/kg immediately after the injection. The mice were killed, and the analysis of serum cholesterol was carried out.

The cholesterol-lowering effect was calculated using the following equation:

$$\text{Cholesterol-lowering effect } (\%) = \frac{C-T}{C-N} \times 100$$

where C = serum cholesterol level (mg/100 ml) in a group of 24 mice measured after injecting the mice with Triton and before treatment with a test compound.

T = serum cholesterol level (mg/100 ml) in a group of 12 of the mice injected with Triton and also treated with a test compound, measured after injection and treatment, and N = serum cholesterol level (mg/100 ml) in a group of 12 untreated mice (i.e. no Triton or test compound administered).

In Table 1, compounds are referred to by the number given below to the Examples.

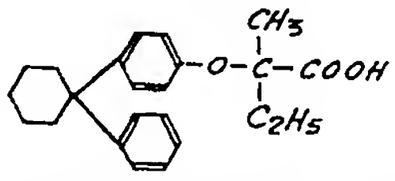
Table 1.

Compound (Example No.)	Cholesterol-lowering effect (%)
1	50
2	48
3	43
4	45
5	45
6	48
7	41
8	44
9	47
10	44
11	38
12	39
15	40
16	43
17	39
19	48
Clofibrate*	14 (a dose of 50 mg/kg)

(* Generic name for ethyl p-chlorophenoxy isobutyrate)

Processes within the present invention are illustrated in more detail by the following Examples, but the invention is not limited to these.

Example 1.



To a mixture of 12 g. of 1-(p-hydroxyphenyl)-1-phenylcyclohexane and 200 g. of methyl ethyl ketone were added 31 g. of potassium hydroxide. 17 G. of chloroform was then added to the mixture with stirring at 20°—30°C, and the mixture was heated at

40°—50°C. for 3 hours to complete the reaction. Thereafter the reaction mixture was concentrated to give a residue. The residue was then dissolved in water, and the resultant solution was treated with active charcoal and acidified with dilute hydrochloric acid to give an oily substance. The oily substance was extracted with ether and the ether solution was extracted again with an aqueous dilute Na_2CO_3 solution. The separated alkaline aqueous layer was acidified and extracted with ether. The ether layer was dried over anhydrous sodium sulfate and concentrated to give a crude product, which was purified by recrystallization from hexane. The desired phenoxycarboxylic acid was obtained, 14 g., m.p., 83°—5°C.

Elemental analysis:

Calculated	(%):	C, 78.37;	H, 8.01
Found	(%):	C, 78.34;	H, 8.10

Examples 2—9.

Using a procedure similar to that described in Example 1, the following compounds were obtained as shown in Table 2.

Table 2

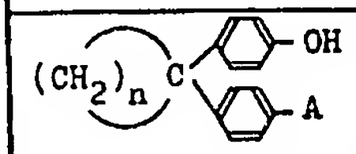
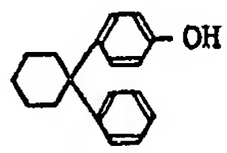
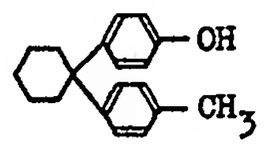
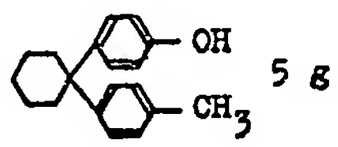
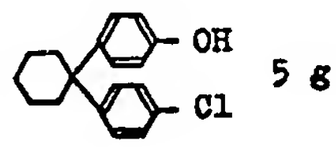
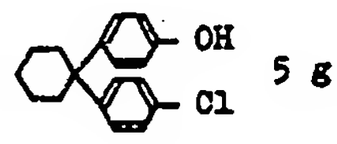
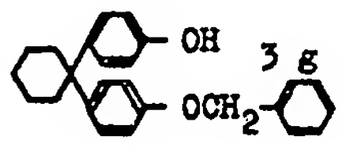
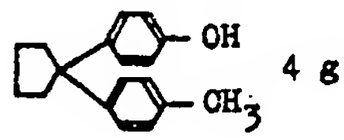
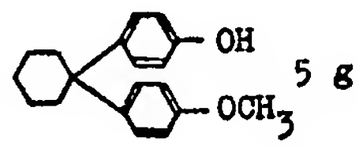
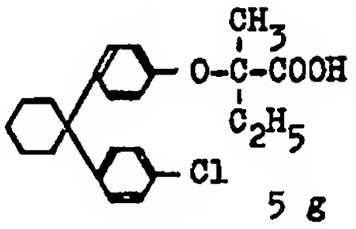
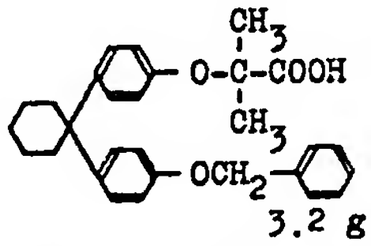
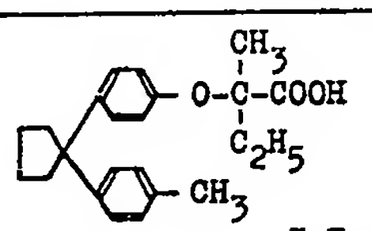
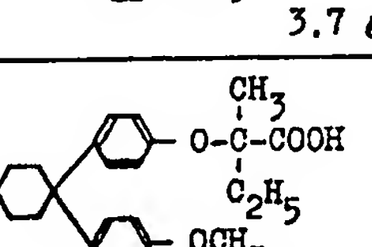
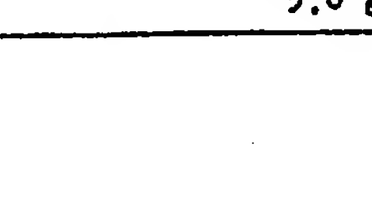
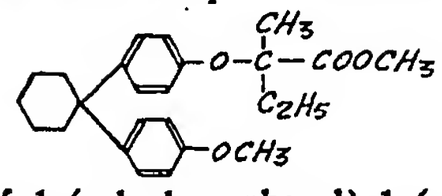
Ex. No.	Starting material			
		$R_1-\overset{O}{\overset{\|}{C}}-R_2$	KOH or NaOH	$CHCl_3$ (temp.) g
2	 3 g	CH_3COCH_3 40 g	KOH 5 g	2.7 g (20°-30°C)
3	 5 g	CH_3COCH_3 100 g	KOH 9.5 g	6.7 g (20°-30°C)
4	 5 g	$CH_3COC_2H_5$ 120 g	KOH 9.5 g	6.7 g (20°-30°C)
5	 5 g	CH_3COCH_3 100 g	KOH 7 g	5 g (20°-30°C)
6	 5 g	$CH_3COC_2H_5$ 120 g	KOH 7 g	5 g (20°-30°C)
7	 3 g	CH_3COCH_3 60 g	KOH 5 g	2.7 g (20°-30°C)
8	 4 g	$CH_3COC_2H_5$ 100 g	KOH 5 g	3.5 g (20°-30°C)
9	 5 g	$CH_3COC_2H_5$ 120 g	KOH 9 g	6 g (20°-30°C)

Table 2 (cont'd)

Reaction time hours (temp.)	Product		
	Chemical structure	Physical property	Elemental analysis Cal (%) Found (%)
2 (50°C)	 3.4 g	m.p. 95.5°-97°C	C 78.07 78.10 H 7.74 7.80
3 (50°C)	 5.5 g	m.p. 133°-4.5°C	C 78.37 78.24 H 8.01 8.04
3 (50°C)	 4.7 g	m.p. 101°-3°C	C 78.65 78.67 H 8.25 8.37
3 (50°C)	 6 g	m.p. 129.5°-131°C	C 70.86 71.08 H 6.76 6.77 Cl 9.51 9.26
3 (50°C)	 5 g	$n_D^{27.5}$ 1.5592	C 71.39 71.43 H 7.03 7.02 Cl 9.16 9.20
3 (50°C)	 3.2 g	m.p. 132°-3°C	C 78.35 78.48 H 7.26 7.28
2 (60°C)	3.7 g	m.p. 94°-5°C	C 78.37 78.32 H 8.01 8.04
3 (50°C)	5.6 g	m.p. 96°C	C 75.36 75.25 H 7.91 7.98

Example 10.



To a mixture of 5 g. of 1-(p-hydroxyphenyl)-1-(p-methoxyphenyl)cyclohexane and 80 ml. of dry toluene was added a toluene suspension of 0.6 g. of sodium hydride under cooling. After stirring the mixture for half an hour, a mixture of 5.5 g. of α-bromo-iso-butyric acid methyl ester and 20 ml. of dry toluene was added dropwise, and the mixture was heated at 60°—80°C for 3 hours. The reaction mixture was cooled and washed with water. The toluene was distilled off, the residue was purified in chromatography column packed with activated alumina. The desired ester was obtained, 4.7 g, n_D^{24} 1.5553.

Elemental analysis:

Calculated (%): C, 75.72; H, 8.13
Found (%): C, 75.64; H, 8.09

Examples 11—15.

Using a procedure similar to that described in Example 10, the following compounds were obtained as shown in Table 3.

Table 3

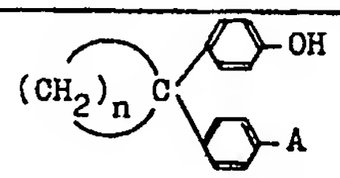
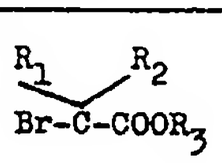
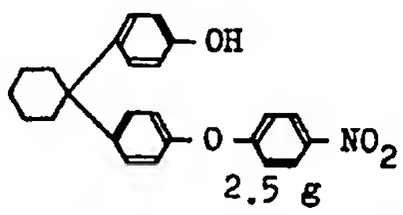
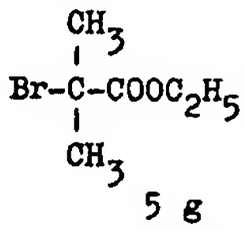
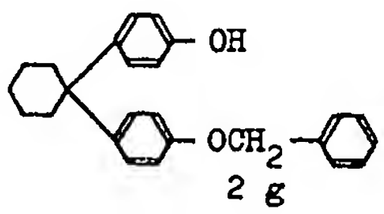
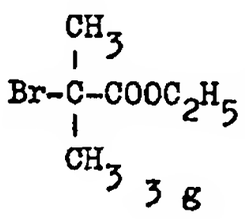
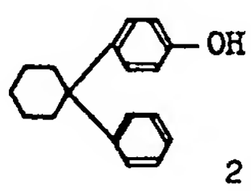
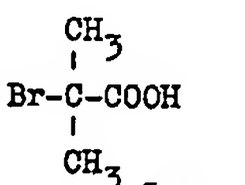
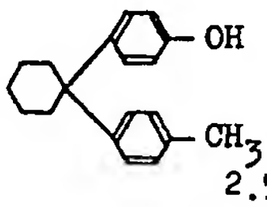
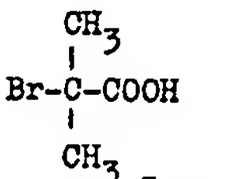
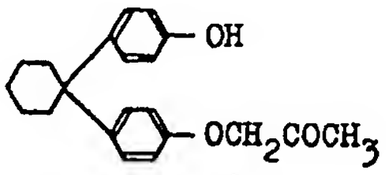
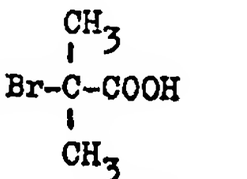
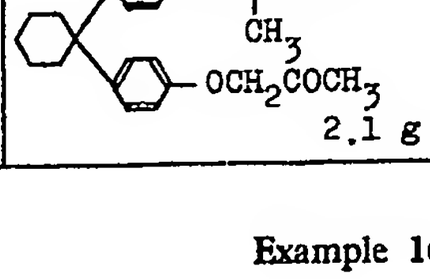
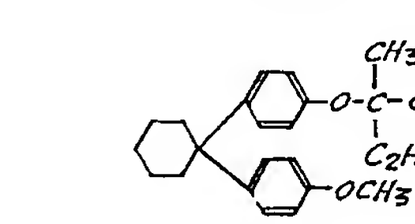
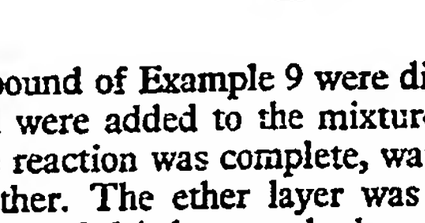
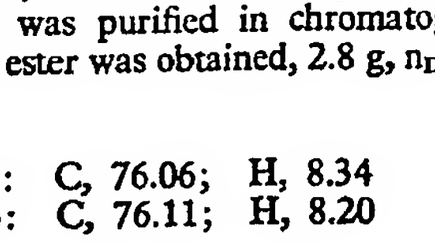
Ex. No.	Starting material		Base	Solvent ml.
				
11	 2.5 g	 5 g	NaH 0.4 g	Toluene 80 ml
12	 2 g	 3 g	NaH 0.3 g	Toluene 50 ml
13	 2 .5 g	 5 g	CH_3ONa 0.6 g	Toluene 70 ml
14	 2.5 g	 5 g	CH_3ONa 0.6 g	Toluene 70 ml
15	 2 g	 5 g	C_2H_5ONa 0.5 g	Toluene 50 ml

Table 3 (cont'd)

Reaction time hours (temp.)	Product		
	Chemical structure	Physical property	Elemental analysis Cal (%) Found (%)
6 hours (70°-80°C)	 2.6 g	n_D^{25} 1.5899	C 71.55 71.41 H 6.61 6.74 N 2.78 2.90
6 hours (80°C)	 2.4 g	m.p. 57°C	C 78.78 78.96 H 7.68 7.56
6 hours (80°C)	 2.6 g	m.p. 95°-96°C	C 78.07 78.04 H 7.74 7.70
6 hours (80°C)	 2.8 g	m.p. 133°-4°C	C 78.37 78.31 H 8.01 8.05
6 hours (80°C)	2.1 g	n_D^{26} 1.5523	C 73.14 73.15 H 7.37 7.37

Example 16.

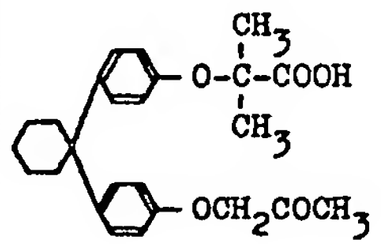
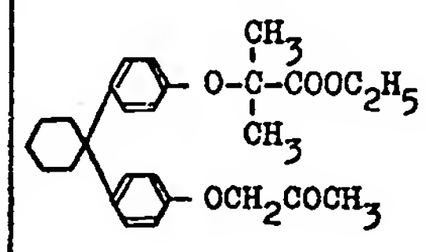
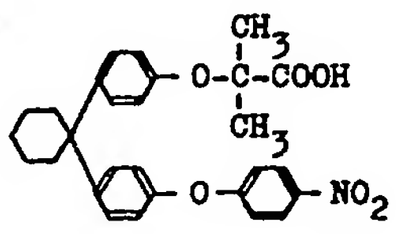
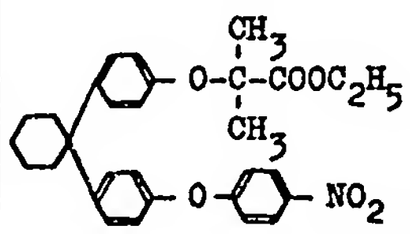
3 G. of the compound of Example 9 were dissolved in 30 ml .of 99% ethanol. Two drops of sulfuric acid were added to the mixture, and the reaction mixture was heated for 6 hours. After the reaction was complete, water was added and the reaction product was extracted with ether. The ether layer was washed with water and then with an aqueous alkali solution, and dried over anhydrous sodium sulfate. The ether was distilled off, and the residue was purified in chromatography column packed with activated alumina. The desired ester was obtained, 2.8 g, n_D^{25} 1.5559.

Elemental analysis:
Calculated (%): C, 76.06; H, 8.34
Found (%): C, 76.11; H, 8.20

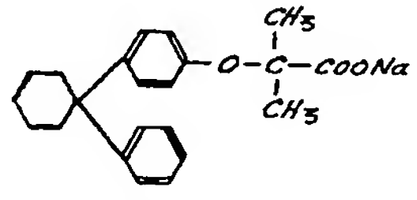
Example 17—18.

Using a method similar to that of Example 12, the following compounds were obtained as shown in Table 4.

Table 4

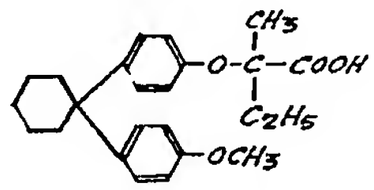
Example No.	Starting material			Reaction time hours (temp.)	Product		
	Phenoxycarboxylic acid (g.)	Alcohol (ml.)	H_2SO_4 (drops)		Phenoxycarboxylic acid ester (g.)	Physical proparty	Elemental analysis Cal(%) Found(%)
17	 2 g.	99 % EtOH (30 ml)	2 (drops)	7 hrs (reflux)	 1.7 g	n_D^{25} 1.5496	C 73.94 73.84 H 7.82 7.85
18	 1.5 g	99 % EtOH (30 ml)	2 (drops)	6 hrs. (reflux)	 1.3 g	n_D^{26} 1.5898	C 71.55 71.47 H 6.61 6.68 N 2.78 2.71

Example 19.



The carboxylic acid obtained in Example 2 was treated with a 10%-NaOH aqueous solution with gentle heating to yield colourless plates which were slightly soluble in water, m.p. > 200°C.

Example 20.

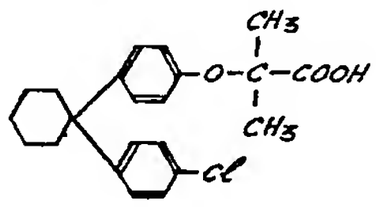


2 G. of the compound of Example 16 were dissolved in 30 ml. of methanol and 3 ml. of a 20% aqueous NaOH solution were added to the mixture. The reaction mixture was stirred for 5 hours at room temperature. After neutralizing the mixture with dilute hydrochloric acid, the reaction mixture was concentrated to give an oily substance. The oily substance was extracted with ether and the ether solution was extracted with an aqueous dilute Na_2CO_3 solution. The separated alkaline aqueous layer was acidified and extracted with ether. The ether layer was dried over anhydrous sodium sulfate and concentrated to give a crude product, which was purified by recrystallization from hexane. The desired phenoxycarboxylic acid was obtained, 1.7 g., m.p. 95°C.

Elemental analysis:
Calculated (%): C, 75.36; H, 7.91
Found (%): C, 75.29; H, 7.88

Using a method similar to that of Example 20, the following products were obtained.

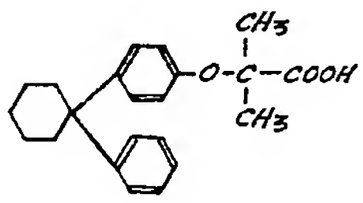
Example 21.



m.p. 129°—131°C.

Elemental analysis:
Calculated (%): C, 70.86; H, 7.67; Cl, 9.51
Found (%): C, 70.94; H, 7.58; Cl, 9.44

Example 22.

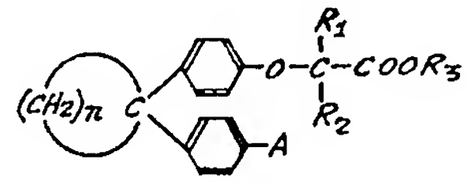


m.p. 96°—97°C.

Elemental analysis:
Calculated (%): C, 78.07; H, 7.74
Found (%): C, 78.04; H, 7.81

WHAT WE CLAIM IS:—

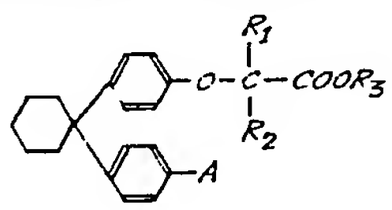
1. A substituted phenoxycarboxylic acid derivative of the formula,



(I)

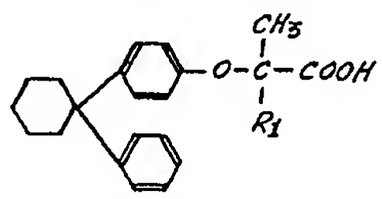
wherein R_1, R_2 and R_3 are each independently a hydrogen atom or a C_1—C_4 alkyl group, n is 4, 5 or 6; and A is a hydrogen atom, a halogen atom, a C_1—C_4 alkyl group, a C_1—C_4 alkoxy group, an optionally substituted aryloxy group, an aralkoxy group or a C_2—C_5 alkanoyloxy group, or a pharmaceutically acceptable salt thereof.

2. A substituted phenoxycarboxylic acid derivative of the formula,



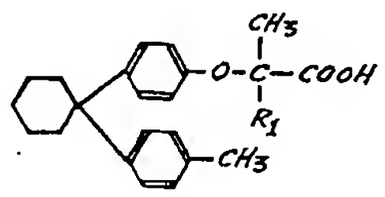
wherein R_1 and R_2 are each independently a methyl or ethyl group, R_3 is a hydrogen atom, or a methyl or ethyl group, and A is a hydrogen atom, a halogen atom, a C_1—C_4 alkyl group, a C_1—C_4 alkoxy group, an optionally substituted aryloxy group, an aralkoxy group or a C_2—C_5 alkanoyloxy group.

3. A substituted phenoxycarboxylic acid derivative of the formula,



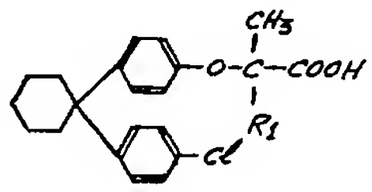
wherein R_1 is a methyl or ethyl group.

4. A substituted phenoxycarboxylic acid derivative of the formula,



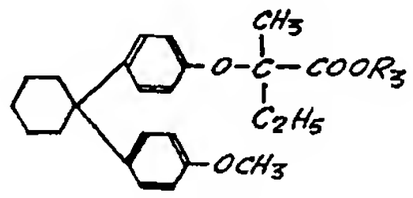
wherein R_1 is a methyl or ethyl group.

5. A substituted phenoxycarboxylic acid derivative of the formula,



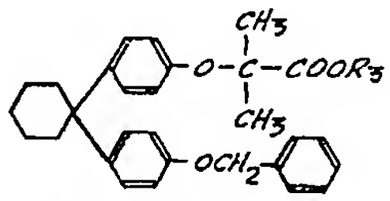
wherein R_1 is a methyl or ethyl group.

6. A substituted phenoxycarboxylic acid derivative of the formula,



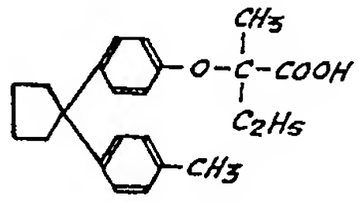
wherein R_3 is a hydrogen atom, or a methiyl or ethyl group.

7. A substituted phenoxycarboxylic acid derivative of the formula,

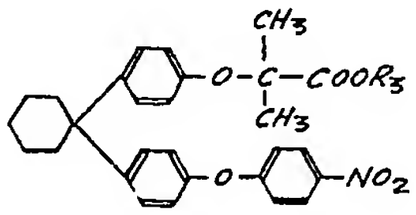


wherein R_3 is a hydrogen atom or an ethyl group.

8. A substituted phenoxycarboxylic acid derivative of the formula,

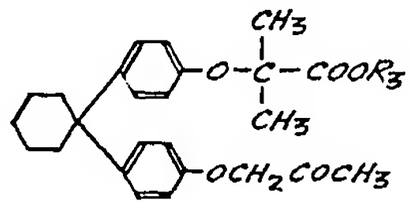


9. A substituted phenoxycarboxylic acid derivative of the formula,



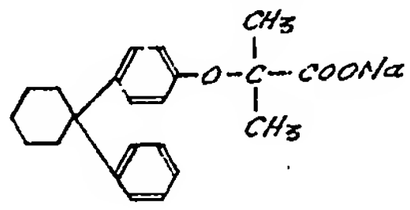
wherein R_3 is a hydrogen atom or an ethyl group.

10. A substituted phenoxycarboxy acid derivative of the formula,

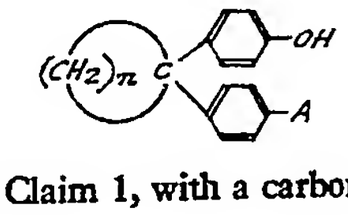


wherein R_3 is a hydrogen atom or an ethyl group.

11. A substituted phenoxycarboxylic acid derivative of the formula,



12. A process for producing a substituted phenoxycarboxylic acid derivative within the formula given and defined in Claim 1, which includes reacting a phenol derivative of the formula,



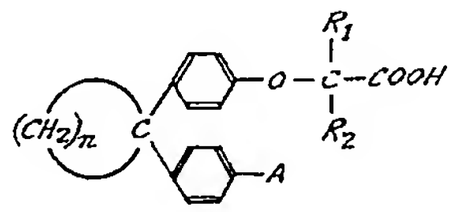
(II)

wherein A and n are as defined in Claim 1, with a carbonyl compound of the formula,

(III)

$$R_1—CO—R_2$$

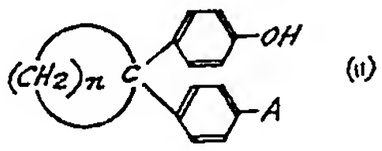
wherein R_1 and R_2 are as defined in Claim 1, and chloroform in the presence of an alkali to yield a substituted phenoxycarboxylic acid derivative of the formula,



(Ia)

wherein R_1, R_2, A and n are as defined in Claim 1.

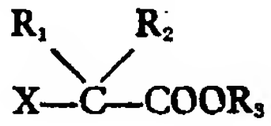
13. A process for producing a substituted phenoxycarboxylic acid derivative of the formula given and defined in Claim 1, which includes reacting a phenol derivative of the formula,



(II)

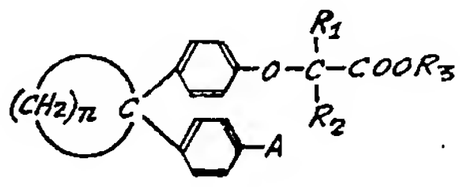
wherein A and n are as defined in Claim 1, with a carboxylic acid derivative of the formula,

(IV)

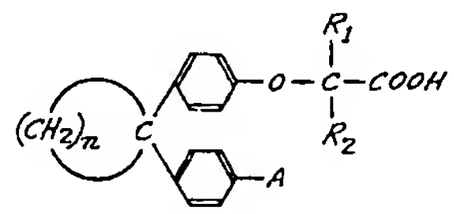


wherein X is a halogen atom or a hydroxyl group and R_1, R_2 and R_3 are as defined in Claim 1, and further, optionally, esterifying or hydrolyzing the resulting product, to yield a substituted phenoxycarboxylic acid derivative of the formula (I).

14. A process for producing a substituted phenoxycarboxylic acid derivative of the formula,

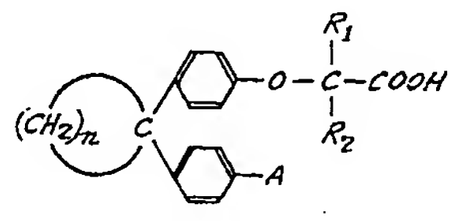


wherein R_1, R_2, A and n are as defined in Claim 1, and R_3 is a C_1—C_4 alkyl group, which includes esterifying a substituted phenoxycarboxylic acid of the formula,

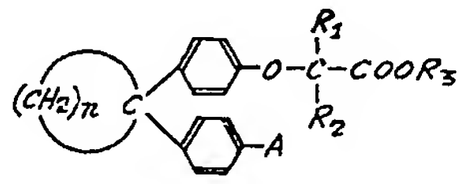


wherein R_1, R_2, A and n are as defined in Claim 1, or a reactive derivative thereof, with an esterifying agent.

15. A process for producing a substituted phenoxycarboxylic acid derivative of the formula,



wherein R_1, R_2, A and n are as defined in Claim 1, which includes hydrolyzing an ester of a substituted phenoxycarboxylic acid of the formula,



wherein R_1, R_2, A and n are as defined in Claim 1, and R_3 is a C_1—C_4 alkyl group.

16. A method of lowering an elevated cholesterol or lipid level in the blood of a non-human animal, which includes administering to the animal a substituted phenoxycarboxylic acid derivative of the formula given and defined in Claim 1 or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition containing a substituted phenoxycarboxylic acid derivative of the formula given and defined in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

18. Substituted phenoxycarboxylic acid derivatives of the formula (I) given and defined in Claim 1, which are specifically disclosed herein.

19. Processess according to any one of Claims 12 to 15 for preparing a substituted phenoxycarboxylic acid derivative substantially as herein described and exemplified.

20. Substituted phenoxycarboxylic derivatives whenever prepared by a process according to any one of Claims 12 to 15 and 19.

MEWBURN ELLIS & CO.,
Chartered Patent Agents,
70/72 Chancery Lane,
London WC2A 1AD.
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1975.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.